# "DEVELOPMENT AND VALIDATION OF STABILITY INDICATING ANALYTICAL METHODS FOR DETERMINATION OF NEW DRUGS AND FORMULATIONS"

**A SYNOPSIS**
submitted for the consideration of
**REGISTRATION**

**for the Degree of *Doctor of Philosophy (Ph.D.)***
in the subject of
***Pharmaceutical Chemistry***
under the Faculty of
***Pharmaceutical Sciences and Technology***
of

स्वामी रामानंद तीर्थ
मराठवाडा विद्यापीठ,नांदेड.

## SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED

by

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**2016**

# SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED

## PROFORMA FOR REGISTRATION OF TOPIC FOR Ph.D.

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| **3.** | **COURSE OF STUDY AND SUBJECT** | **:** | Ph.D. (Pharmaceutical Chemistry) |
| **4.** | **DATE OF ADMISSION TO THE COURSE** | **:** | |
| **5.** | **TITLE OF RESEARCH TOPIC** | **:** | **"Development and Validation of Stability Indicating Analytical Methods for Determination of New Drugs and Formulations"** |

## 6. OBJECTIVES OF RESEARCH TOPICS:

### 6.1 Main Objectives:

1. Develop and validate analytical methods for active pharmaceutical ingredients.
2. Formulation Development of Active pharmaceutical Ingredients.
3. The degradation will be performed by forced decomposition studies.
4. Formulations of selected drugs will be subjected to accelerated stability testing.

## 7. REVIEW OF LITERATURE:

1. **Saranjit Singh, Baljinder Singh, Rakesh Bahuguna, Lalit Wadhwa, Rahul Saxena**, A stability-indicating HPLC method was developed for analysis of the drug Ezetimibe in the presence of the degradation products. It involved a C-8 column and a mobile phase composed of ammonium acetate buffer (0.02 M, pH adjusted to 7.0 with ammonium hydroxide) and acetonitrile, which was pushed through the column in a gradient mode. The detection was carried out at 250 nm. The method was validated for linearity, range, precision, accuracy, specificity, selectivity and intermediate precision.[1]

2. **Sanjay Motwani, Roop Khar, Farhan Ahmad, Shruti Chopra**, A simple, sensitive, selective, precise and stability-indicating high-performance thin-layer chromatographic (HPTLC) method for densitometric determination of Moxifloxacin both as a bulk drug and from pharmaceutical formulation was developed and validated as per the International Conference on Harmonisation (ICH) guidelines. Densitometric analysis of Moxifloxacin was carried out in the absorbance mode at 298 nm. In addition the pH-rate profile for

degradation of Moxifloxacin in constant ionic strength buffer solutions within the pH range 1.2–10.8 was studied.[2]

3. **B. Mallikarjuna Rao, Sivaiah Sangaraju, M.K. Srinivasu, P. Madhavan, M. Lalitha Devi, P. Rajendra Kumar,** Performed Forced degradation studies on bulk sample of Rizatriptan benzoate using acid (0.5N hydrochloric acid), base (0.1N sodium hydroxide), oxidation (3.0% hydrogen peroxide), water hydrolysis, heat (60 °C) and photolytic degradation. Mild degradation of the drug substance was observed in base hydrolysis and considerable degradation observed during oxidative stress. The stress sample solutions were assayed against the qualified reference standard of Rizatriptan benzoate and the mass balance in each case was close to 99.7% indicating that the developed method is stability indicating.[3]

4. **Ali Reza Fakhari, Afshin Rajabi Khorrami, Mojtaba Shamsipu,** A stability-indicating high-performance thin-layer chromatography (HPTLC) method was developed and validated for simultaneous determination of steroidal hormones levonorgestrel and ethinyloestradiol both in bulk drug and in low-dosage oral contraceptives. Densitometric analysis of the drugs was carried out in the reflectance mode at 225 nm by using a computer controlled densitometric scanner. The calibration curves of levonorgestrel and ethinyloestradiol were linear in the range of 200–800 and 40–160 ng per spot, respectively.[4]

5. **Adel Mishal, Diana Sober**, A selective, precise and accurate isocratic RP-HPLC method has been developed and validated for the simultaneous determination of Metronidazole benzoate (MB), Diloxanide furoate (DF), methyl paraben (MPn) and propyl paraben (PPn) in suspension. The four analytes were well resolved from the degraded solutions peaks. The excepients present in the formulation do not interfere with the assay procedure. The proposed method can be

utilised for the routine analysis of the four analytes in pharmaceutical dosage form.[5]

6. **Vijay Kumar, Hemant Bhutani, Saranjit Singh,** Performed Stability-indicating HPLC method for simultaneous determination of Ampicillin and Cloxacillin in combination drug products. Ampicillin and Cloxacillin were degraded together under different stress test conditions prescribed by International Conference on Harmonisation. The method was validated for linearity, precision, accuracy, specificity and selectivity. It was also compared with the assay procedures given in British Pharmacopoeia for individual drugs. Similar results were obtained, indicating that the proposed single method allowed selective analysis of both Ampicillin and Cloxacillin, in the presence of their degradation products formed under a variety of stress conditions. Ampicillin and Cloxacillin were degraded together under different stress test conditions prescribed by International Conference on Harmonisation. The samples so generated were used to develop a stability-indicating high performance liquid chromatographic (HPLC) method for the two drugs.[6]

7. **Gaetano Ragno, Antonio Garofalo, Claudio Vetuschi**, developed a derivative spectrophotometric method for the simultaneous determination of Amlodipine and its pyridine photodegradation product. The method could usefully be applied to routine quality control of pharmaceutical formulations containing Amlodipine.[7]

8. **Shaza Shantier, Elrasheed Gadkariem, Mohamed Adam, Magdi Mohamed**, The degradation behavior of cefquinome sulphate in alkaline medium at different temperatures was investigated using both first derivative spectrophotometric and HPLC methods. The drug degradation was found to be pH and temperature dependant. Stability-

indicating thin-layer chromatographic method for the separation of the drug and its alkaline hydrolysis product has been developed.[8]

9. **Hesham Salem, Azza Aziz Moustafa, Maha Hegazy and Omnia Ali**, A Simple, sensitive, selective and precise stability-indicating thin-layer chromatographic (TLC) and high-performance liquid chromatographic (HPLC) methods for the determination of Buflomedil (BFM) in pharmaceutical tablets were developed and validated as per the International Conference on Harmonisation guidelines. Buflomedil was exposed to acid hydrolysis and analyzed by the proposed methods in presence of its degradation products.[9]

10. **Lucas Chierentin and Hérida Regina Nunes Salgado,** A stability-indication high performance liquid chromatographic method has been developed for the determination of Norfloxacin in tablet dosage forms. Linearity, system suitability, precision, sensitivity, selectivity, specific, and robustness were established by International Conference Harmonisation guidelines. For stress studies the drug was subjected to photolysis, oxidation, acid, alkaline and neutral conditions. The analytical conditions and the solvent developed provided good resolution within a short analysis time.[10]

11. **Kasa Srinivasulu, Mopidevi Narasimha Naidu, Kadaboina Rajasekhar, Murki Veerender, and Mulukutla Venkata Suryanarayana,** developed and validated simple, sensitive, stability indicating HPLC method and assay determination of Bortezomib. Stability indicating power of the method was established by forced degradation experiments and mass balance study. The stability tests were also performed on drug substances as per ICH norms.[11]

## 8. MATERIAL AND METHODS

1. Selection of drug and excipients.
2. Procurement of drug and excipients.
3. Preformulation studies:

   A) Raw material characterisation

   - Characterisation of drug.
   - Characterisation of excipients.

   B) Structural Characterisation

   - UV
   - FTIR

   C) Physicochemical Characterisation

   - Solubility studies.
   - pH determination.
4. Chromatographic Development

   A) HPLC

   B) HPTLC

## 9. CURRENT STATUS OF STABILITY STUDIES:

1. US Patent (US- 8529949 B2) AripipraZole tablets having reduced dissolution profile variability upon storage.
2. US Patent (US-20150094345 A1) a pharmaceutical formulation containing Ramipril with improved stability.

## 10. DURATION OF WORK

| Sr. No. | WORK | PERIOD |
|---|---|---|
| 1. | Literature survey | 6 Months |
| 2. | Procurement and selection of drug/drug combinations for the method development | 2 Months |
| 3. | Characterisation of procured ingredients. | 4 Months |
| 4. | Development of chromatographic methods for selected drug candidates | 8 Months |
| 5. | Development of stress degraded samples of individual drugs; confirming suitability of the methods developed above | 8 Months |
| 6. | Validation of developed method as per ICH Guidelines | 2 Months |
| 7. | Accelerated stability testing of formulation | 6 Months |
| | **Total Duration of Project** | **36 Months** |

## 11. REFERENCES:


1. Saranjit Singh, Baljinder Singh, Rakesh Bahuguna, Lalit Wadhwa, Rahul Saxena. Stress degradation studies on Ezetimibe and development of a Validated stability-indicating HPLC assay. ***J. Pharm. Biomed. Anal.*** 41 (2006) 1037- 1040.

2. Sanjay Motwani, Roop Khar, Farhan Ahmad, Shruti Chopra. Application of a validated stability-indicating densitometricthin-layer chromatographic to stress degradation studies on Moxifloxacin. ***Analytica Chimica Acta*** 582 (2007) 75-82.

3. B. Mallikarjuna Rao, Sivaiah Sangaraju, M.K. Srinivasu, P. Madhavan, M. Lalitha Devi, P. Rajendra Kumar. Development and validation of a specific stability indicating High performance liquid chromatographic method for Rizatriptan benzoate. ***J. Pharm. Biomed. Anal.*** 41 (2006) 1146-1151.

4. Ali Reza Fakhari, Afshin Rajabi Khorrami, Mojtaba Shamsipu. Stability-indicating high-performance thin-layer chromatographic determination of Levonorgestrel and Ethinyloestradiol in bulk drug and in low-dosage oral contraceptives. ***Analytica Chimica Acta*** 572 (2006) 237-242.

5. Adel Mishal, Diana Sober. Stability indicating reversed-phase liquid chromatographic determination of Metronidazole benzoate and Diloxanide furoate as bulk drug and in suspension dosage form. ***J. Pharm. Biomed. Anal.*** 39 (2005) 819-823.

6. Vijay Kumar, Hemant Bhutani, Saranjit Singh. ICH guidance in practice: Validated stability-indicating HPLC method for simultaneous determination of ampicillin and cloxacillin in combination drug products. ***J. Pharm. Biomed. Anal.*** 43 (2007) 769-777.

7. Gaetano Ragno, Antonio Garofalo, Claudio Vetuschi. Photodegradation monitoring of Amlodipine by Derivative spectrophotometry, ***J. Pharm. Biomed. Anal.*** 27 (2002) 19-24.

8. Shaza Shantier, Elrasheed Gadkariem, Mohamed Adam, Magdi Mohamed. Development of Stability-Indicating Methods for Cefquinome Sulphate. ***Int. J. Biomed. Sci.*** 9 (2013) 162–167.

9. Hesham Salem, Azza Aziz Moustafa, Maha Hegazy and Omnia Ali. Stability Indicating Validated Chromatographic Methods for Determination of Buflomedil in Presence of its Degradation Products. ***Pharm. Anal. Acta***. 4:233 (2013) 1-5.

10. Lucas Chierentin and Hérida Regina Nunes Salgado. Development and Validation of a Simple, Rapid and Stability-Indicating High Performance Liquid Chromatography Method for Quantification of Norfloxacin in a Pharmaceutical Product. ***J. Chromat Separation Techniq*** *4:2* (2013) 1-5.

11. Kasa Srinivasulu, Mopidevi Narasimha Naidu, Kadaboina Rajasekhar, Murki Veerender, and Mulukutla Venkata Suryanarayana. Development and Validation of a Stability Indicating LC Method for the Assay and Related Substances Determination of a Proteasome Inhibitor Bortezomib. Chromatography Research International. (2013) 1-14.

12. ICH, Q2A (R1), Stability testing of new drug substances and products, in: International Conference on Harmonisation, IFPMA, Geneva, 2003.

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| **13.** | **REMARKS OF THE GUIDE** | **:** | |
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